In fatal COVID-19, the immune response can control the virus but kill the patient

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COVID-19 is often a biphasic illness with an initial phase of upper respiratory symptoms that can rapidly progress to profound hypoxemia and respiratory failure. Postmortem studies of severe COVID-19 reveal diffuse alveolar damage, hyaline membranes, and thrombi, with varying degrees of inflammation and types of cellular infiltrates (1–5). Now, with their autopsy study of early victims of the pandemic in China, Wu et al. (6) provide important insights into the inflammatory pathways that lead to severe COVID-19 pneumonia. Their extensive transcriptional and proteomic analyses of lung tissue from patients with severe pneumonia reveal signatures indicative of a neutrophil-driven inflammatory response without evidence of much active viral proliferation. These findings indicate that the pathogenesis of late severe COVID-19 pneumonia involves a dysregulated immune response, rather than direct viral damage.

The identification of neutrophil-driven inflammatory pathways by Wu et al. (6) is consistent with reports of hyaline membrane formation, neutrophils, neutrophil extracellular traps (NETs), and platelet-induced immunopathology in COVID-19 lung damage (7–9). Another critical finding is the paucity of viral sequences in the lung tissues examined, implying little or no viral replication (6). In fact, it is possible that the few viral reads identified represent residual nucleic acid in tissue from nonviable virus. One recent autopsy study did not identify SARS-CoV2 in lung tissue of patients with advanced disease (10), another found virus in the lungs of patients who died during acute disease (11), and another found that viral loads correlated with the inflammatory response and death; those with high viral loads expressed high levels of interferon (IFN)-stimulated genes with minimal lung damage, whereas those with low viral loads had extensive lung damage and low IFN-stimulated gene expression (5). Thus, the immune response during severe COVID-19 pneumonia may progress from inhibition of viral replication to inflammatory damage that continues despite viral control.

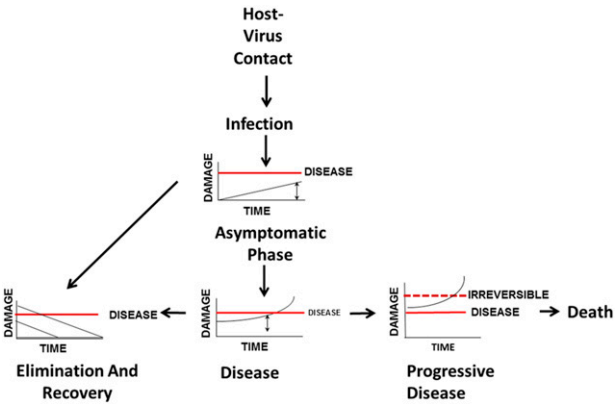

Fig. 1. Proposed scheme for the progression and outcomes of COVID-19 from the viewpoint of the damage–response of pathogenesis (24). According to the damage–response framework, the relevant outcome is the amount of host damage endured by the host during the host–microbe interaction. Considering damage as a function of time, death occurs in those individuals who suffer irreparable tissue damage, which appears to be mediated largely by the inflammatory response to SARS-Cov-2.

The patients in the Wu et al. (6) report had severe pneumonia with a fibrotic response and transcriptional and histological evidence of neutrophil-driven inflammation. There was also a paucity of cytokine-driven inflammatory signatures. This is consistent with another study in which a subset of patients who died early in the course of COVID-19 had high levels of proinflammatory cytokines but those who died late in disease had low levels (5). This is important because therapeutic strategies intended to inhibit cytokines and cytokine activation may not be beneficial in patients with low viral loads and a paucity of proinflammatory cytokines. Given the absence of virus in postmortem lung tissue in the Wu et al. (6) cohort, the observed pulmonary fibrotic changes are likely "postinfectious" (12), reinforcing the paradigm that the immune response can drive host damage in the absence of active microbial infection (1).

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As Wu et al. note (6), their finding of very few to no detectable viral sequences in the lungs may help explain the lack of efficacy of remdesivir in patients with late disease (13). In contrast, the finding of marked neutrophil activation and infiltrates may help explain the efficacy of corticosteroids in patients with severe disease. By inhibiting inflammation, these powerful antiinflammatory drugs may protect lung tissue so it can maintain its ability to conduct gas exchange. The report of Wu et al. (6) provides strong evidence that neutrophil activation and NETs play a role in the development of fibrotic lung damage in severe COVID-19. Therefore, the benefit of glucocorticoids in such patients may be a function of their capacity to inhibit neutrophil-mediated inflammation (14), rather than nonspecific effects on inflammation. However, glucocorticoids can also exert proinflammatory effects on neutrophils, including inhibition of apoptosis, which may help explain why they are not beneficial early in COVID-19 disease. Thus, the transcriptional signatures Wu et al. report (6) may inform the discovery of neutrophil-associated biomarkers to guide glucocorticoid therapy in COVID-19 more precisely. However, given the different inflammatory profiles of patients with severe disease who had different viral burdens (5), biomarkers or signatures that reflect the tissue inflammatory response as a function of the viral burden may be necessary to identify therapies that confer the most benefit and the least risk.

Wu et al. (6) also report colonic inflammation without obvious signs of gastrointestinal disease in their cohort. This highlights the fact that severe COVID-19 is a systemic disease even though its life-threatening manifestations are mainly the result of pulmonary compromise and thrombotic complications in the lungs, kidneys, and brain. Importantly, the data of Wu et al. (6) reflect the immune response at the end of a pathogenic process when pulmonary fibrosis was underway. In this regard, the finding that IL-6 was not upregulated does not contradict findings from other studies showing elevated levels of this cytokine at earlier stages of disease (15). More research is needed to understand the interplay between the antiviral response, beneficial inflammation, and the onset of immune dysregulation that culminates in irreparable damage to pulmonary tissue.

Given that the findings of Wu et al. (6) capture the final state of fatal COVID-19, it is now possible to outline a comprehensive picture of the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most infections are asymptomatic or minimally symptomatic (16). Thus, infection is much more common than disease (Fig. 1). However, in a significant minority of individuals, the virus affects the lower airways and causes a pneumonia that can range from mild to severe. For some, this phase is systemic, with involvement of various organs including the kidneys, brain, and gastrointestinal tract. In each phase of disease, the outcome of infection is a function of viral load and quantitative and qualitative aspects of the immune response. In some people, particularly those with chronic conditions that impair the immune response, persistent viral replication in the lungs and possibly other organs triggers an exuberant inflammatory response that damages host tissues and impairs organ function. This is manifested clinically as dyspnea and hypoxia. For some, the immune response induces viral elimination, and the damage is repairable, leading to recovery, although a subset of these patients may have persistent symptoms and findings (17). However, for others, the immune response is dysregulated and leads to tissue damage that results in pulmonary failure. In the days prior to modern medicine and the availability of interventions to improve oxygenation, such as ventilator support and extracorporeal membrane oxygenation, this would have resulted in rapid demise. Respiratory support allows many to survive this crisis, but, for others, persistent and progressive damage leads to organ failure and death. Among survivors, pulmonary fibrosis could complicate recovery and trigger long-term consequences by diminishing pulmonary capacity. Notably, there may be another population of patients who respond to SARS-CoV-2 differently. These patients have evidence of chronic viral infection and exhibit symptoms of smoldering disease without marked pulmonary compromise. Some such patients have immune deficiencies (18) that may compromise their ability to induce viral elimination but spare them from the inflammatory dysregulation that leads to respiratory failure.

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Early in the disease process, when the virus replicates in the upper respiratory tract, therapies that interfere with viral replication, such as antiviral drugs and specific antibodies, may abort the progression of disease by reducing viral load, which, in turn, reduces immune stimulation and the danger of progressive tissue-damaging inflammation. Consistent with this view, both remdesivir and convalescent plasma, which have direct antiviral effects, hasten improvement when administered before severe symptoms emerge (13, 19, 20). However, once severe inflammation takes hold, antiinflammatory agents are likely needed. This is supported by strong evidence that dexamethasone reduces mortality in patients with severe COVID-19 disease who require respiratory support (21). While interventions that support pulmonary function provide an opportunity for tissue repair, there is a need for new therapies that inhibit or reverse inflammatory damage.

What determines the outcome of the interaction between SARS-CoV-2 and the human host? Although certain preexisting conditions increase the likelihood of severe disease, and the findings of Wu et al. (6) hold promise for the identification of inflammatory biomarkers that might guide therapy, we still may not be able to predict the outcome of SARS-CoV-2 at the level of the individual. This is because numerous variables such as the size of infective inoculum, immunological history, genetics, and the vagaries of chance interact to produce outcomes that defy prediction (22). For example, a cohort of patients with severe COVID-19 were found to have autoantibodies to type I IFN, which could interfere with the early IFN response to SARS-CoV-2 infection (23). Another important message from the study of Wu et al. (6) is that efforts to identify those at highest risk for severe COVID-19 and death will need to focus on the variables that trigger organ-damaging immune responses.

In summary, Wu et al. (6) provide insights reinforcing the critical point that, despite controlling the virus, the immune response may also result in irreparable damage that is fatal. Although this notion was already part of the emerging understanding of the pathogenesis of this disease (1), firm evidence from autopsy studies demonstrating that people die with inflammation and a very low viral load moves this concept from hypothesis to fact, with great consequences for directing clinical care and designing new therapies.

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